# PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

X16723

# PCT

## WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
*(day/month/year)* see form PCT/ISA/210 (second sheet)

26 DEC / 26 JAN 2006

Applicant's or agent's file reference
see form PCT/ISA/220

**FOR FURTHER ACTION**
See paragraph 2 below

| International application No | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/US2005/009301 | 17.03.2005 | 26.03.2004 |

International Patent Classification (IPC) or both national classification and IPC
C07D495/04, C07D471/04, A61K31/44, A61P3/04, A61P9/00, A61K31/47, A61K31/435

Applicant
ELI LILLY AND COMPANY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220

3 For further details, see notes to Form PCT/ISA/220.

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**Box No. I Basis of the opinion**

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 12-18

because:

☒ the said international application, or the said claims Nos. 12-18 with regard to IA relate to the following subject matter which does not require an international preliminary examination *(specify)*:

**see separate sheet**

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

| | | |
|---|---|---|
| the written form | ☐ | has not been furnished |
| | ☐ | does not comply with the standard |
| the computer readable form | ☐ | has not been furnished |
| | ☐ | does not comply with the standard |

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

**Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes. | Claims | 5-7 |
| | No: | Claims | 1-4,8-20 |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1-20 |
| Industrial applicability (IA) | Yes | Claims | 1-11,19,20 |
| | No: | Claims | |

2. Citations and explanations

**see separate sheet**

**Box No. VIII Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**re Item III:**

1. Claims 12-18 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(I) PCT).

**re Item V:**

1. The application relates to fused 4-aminopiperidines of the general formula (I), which have utility for treating pathological states due to dyslipidemia, for example atherosclerosis, hypercholesterolemia, coronary hear diseases or other diseases regulated by cholesterol ester transfer protein (CETP).

   The relevant prior art has been cited in the search report.
   D1: EP-A-0 992 496 (PFIZER PRODUCTS INC) 12 April 2000 (2000-04-12)
   D2: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 2003, FUKUMOTO, MASASHI ET AL: "Preparation of 5,6,7,8-tetrahydropyrido[2,3-d]pyrimidine and 6,7,8,9-tetrahydropyrimido[4,5-b]azepine derivatives as G protein-coupled receptor kinase (GRK) inhibitors" XP002333707 retrieved from STN Database accession no. 2003:884545
   D3: WO 00/17166 A (PFIZER PRODUCTS INC; DENINNO, MICHAEL, PAUL; MULARSKI, CHRISTIAN, JAME) 30 March 2000 (2000-03-30)
   D4: EP-A-0 818 197 (BAYER AG) 14 January 1998 (1998-01-14)
   D5: DATABASE BEILSTEIN BEILSTEIN CROSSFIRE INSTITUT ZUR FOERDERUNG DER CHEMISCHEN WISSENSCHAFTEN, DE; BRN 5584498 1993, XP002333708
   D6: GB-A-1 515 540 (LABAZ) 28 June 1978 (1978-06-28)

2. Novelty
   D1 discloses fused tricycles as CETP inhibitors. The class of compounds having the formula I overlap with the present compounds (see R1 is W-X and R3 is Q). Compounds of that genus have been individualised, for instance, in examples 5-17.

By consequence, the present claims 1-4, 8-20, which relate to products wherein two adjacent R5 groups are combined to form a fused 5 or 6 membered ring with ring A, do not meet the requirement of Art. 33(2) PCT.

Similarly, the present compounds overlap with the 6,7-dihydro-pyrido[2,3-d]pyrimidines of D2, which are said to be useful to treat hypercholesterolemia (see the general formula depicted in the abstract and also on page 8 of the description). The individual compounds depicted in the copy of the Chemical Abstracts record fall within the area of overlap, such that the subject-matter of claims 1-4, 8, 11-20 does not meet the requirements of Art. 33(2) PCT.

The tetrahydroquinoline CETP inhibitors of D3 have been disclaimed. The CETP inhibitors of D4 lack the present amino group R4, which in the prior art is substituted for a hydroxy or alkoxy group.

Further novelty destroying products are disclosed in D5 (BRN 5584498) and D6 (examples on pages 9-17).

3. Inventive step

D1-D4 represent the most pertinent prior art documents, because these documents already teach, that fused 4-aminopiperidines are useful to treat pathologies associated with CETP. While tetrahydroquinoline derivatives have been excluded from claim 1, D3 teaches that substituents sticking to the piperidine moiety may be largely varied without deterioration of the activity. From the reading of D1, the skilled person became aware that the present ring A is also not critical to the achieve the desired activity, at least not with regard to steric or electronic constraints at the biological target, because ring A in the form of an monoaromatic or bicyclic fused ring have shown to be active. In the light of the fact, that D1 and D3 share a major structural fragment and also relate to compounds with the same activity, the skilled person would have combined the teaching of these documents. By doing so, he would have considered attractive further modifications of the already varied ring A. As the presently proposed ring structures A exert similar steric and electronic constraints to the biological active site, the skilled person would have expected that the present modifications still would result in CETP active products. Therefore, the products are

considered to be an obvious solution to the problem of providing further compounds, which are useful to treat CETP related pathologies. The subject-matter, which may be regarded as novel, does not appear to have involved an inventive step in the sense of Art. 33(3) PCT.

**re Item VIII:**

1. The subject-matter of claim 1 is not clear with regard to the definition for R1, since this residue has only be defined for the combinations of n=0 and k is not a bond, or n is an integer higher than 0 and k is a bond. No definition has been provided for the combinations, where n=0 and K is a bond, or n is an integer higher than 0 and k is not a bond. Since the scope of the claim cannot be assessed, the requirement of Art. 6 PCT is not met.

2. A reference to claim 1 is missing at the beginning of claim 11.

3. The above cited literature D1, D2, D4-D6 has not been mentioned in the description.